REMARKS

Status of the Claims

Claims 1, 3-6, 8, and 9-24 are pending. Claims 1, 6, 8, 22 and 23 are amended. Claims 25-30 are added. Claims 19-21 are free from any rejection.

No new matter is added in the above amendment.

Examiner Interview Summary

On September 28, 2009, an interview took place between Applicant, Applicant's representative, and Examiner Peselev. The interview is summarized on the Examiner Interview Summary Form prepared by the Examiner and entered in the Record.

The present Response clarifies some previously presented evidence concerning state-of-the-art, USP Amphotericin B formulations and the contaminants contained therein. During the interview, the previous declarations of Dr. Kramer and Dr. Cleary were discussed. Also, the *Journal of Antimicrobial Chemotherapy* publication (which was also an attachment to Dr. Cleary's Declaration of 29 April 2008) was discussed. An additional copy of the article was left with the Examiner for her additional consideration.

As indicated on the Examiner Interview Summary Form, Applicants additionally asserted that the claims comply with the Written Description Requirement, and that their position is supported by case law and USPTO policy.

The Examiner agreed to carefully consider the instant Amendment and Response. The time and attention of the Examiner are greatly appreciated.

Issues Under 35 U.S.C. § 112

Claims 1, 4-6, 17, 18, 21, 22, and 24 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

This rejection has been discussed extensively throughout the Record and was discussed at the interview as well.

Initially, Applicants point out that the above amended claims should clearly comply with the written description requirement. Claims 1, and 6 and 22 are amended to describe the ranges in a similar format to claim 3.[1] Claim 3 is free from this rejection. Further, certain claims describe ranges that are explicitly stated in the Specification and specifically mentioned in the Office Action as being supported by the Specification. Id.

With respect to the Examiner's position concerning an alleged lack of support for ranges including "at least 95%", and "at least 94%", Applicants respectfully submit that said position is not correct. The outstanding Office Action states that " 'greater than 96%' pure does not provide

[1] The Examiner will note that the ranges in the amendment claims may be "broader" that those ranges previously claimed. Why these ranges are free from the cited prior art was discussed during the interview and reiterated in the comments below.

adequate support for the terminology 'at least 95%' and 'at least 94%'". See the Office Action at page 3. However, the Office Action improperly fails to address how the phrase "greater than about 90% pure" does not support for "at least 96%," for example. There are four examples of "substantially pure" in the Specification within this relatively narrow range. One of ordinary skill in the art would certainly understand that "at least 90" includes at least 92, 94, and 95.

There is certainly plenty of support for Applicant's position, both in terms of USPTO policy and case law. Applicants have stated throughout the prosecution of this Application that to satisfy the written description requirement, a patent specification must only describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. The Office Action fails to provide one supported, objective reason stating why one of ordinary skill in the art would reach the conclusion that the present claims are not supported.

It should also be well understood that with the written description requirement, there is no *in haec verba* requirement, so newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. The present Office Action fails to take into account the ranges that one skilled in the art would consider inherently supported by the discussion in the original disclosure, an analysis that is required.

Additionally, in the previous response Applicants compared their position to the one presented in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). There, the ranges

described in the original specification included a range of "25% - 60%" and specific examples of "36%" and "50%." A new claim limitation to "between 35% and 60%" was held to have complied with the description requirement. The Wertheim decision was acknowledged in the Office Action, but the Office Action failed to provide any examples as to why it would not guide the Examiner to withdrawing the present rejection. In the present case, the claimed range is smaller and the number of examples provided is larger than provided in Wertheim. That being the case, Applicants respectfully submit that it is incumbent on the Examiner to provide a detailed, technically supported, objective explanation analysis as to why the present claims are not supported. To date such an analysis has not been provided.

Additionally, as stated in the previous response, the burden is on the Examiner to show non-compliance with the Written Description Requirement. See M.P.E.P. § 2163.04, entitled "Burden on the Examiner with Regard to the Written Description Requirement." The Examiner must have a reasonable basis to challenge the adequacy of the written description. No such basis is provided in the Office Action. The Examiner must establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. No such reasons are provided in the instant Office Action. To the contrary, the Office Action even fails to specifically point out the specific claim features that fail to comply.

Accordingly, Applicant's respectfully submit that this rejection should be withdrawn.

Issues Under 35 U.S.C. § 103

Claims 1, 3-6, 8, and 17-24 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Lopez-Berenstein et al. (US '167) in view of US Patent No. 4,902,789 to Michel et al. (US '789), or US Patent No. 4,308,375 to Tang (US '375). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

These references are discussed extensively in the record and during two interviews. A summary follows:

The primary reference, Lopez-Berenstein patent fails to even address amphotericin B purity. The Office Action even acknowledges that Lopez-Berenstein "...do not disclose purification of amphotericin B." See the Office Action at page 3. On the other hand, Lopez-Berenstein is concerned with encapsulation.

Applicants respectfully submit that this deficiency should not be surprising to one of ordinary skill in the art. As should be clear in the record, for years the usefulness of USP amphotericin B compositions have been compromised by a high incidence of adverse effects [flu-like symptoms (fever, chills, myalgias), capillary leak syndrome (hypotension, decreased organ perfusion), pulmonary congestion, changes in mental status (lethargy, confusion, agitation), renal dysfunction with secondary hypokalemia, hypomagnesemia and anemia, and liver dysfunction]. These adverse reactions are observed in up to seventy percent of treated patients. Despite such drawbacks, traditional USP amphotericin B compositions remain the best or only alternative for critically ill patients. The encapsulation techniques, such as those attempted in the primary reference, were though of as the best way to formulate a safer

amphotericin product.

The Office Action is forced to remedy such a major deficiency of the primary reference by attempting to assert that one would be motivated to combine it with several secondary references based on the overly simplistic theory that "purification… was well known in the art." This is where the trouble begins.

One problem is that one of ordinary skill in the art would realize that the secondary references provide no help in arriving at the present invention. Another problem is that even if combined, the addition of the secondary references would not address the problem discovered by Applicants, that the non-amphotericin polyenes and other soluble compounds should be removed from the parent formulation. The methods of the secondary references fail to accomplish this.

The first secondary reference, Michel et al., includes a purification method, but the one selected is a four-solvent method that results in *improved removal of insoluble content*, an improvement that corresponded with a "yield" of 97%. Their improvement is one of a more consistent crystallization of product. Applicants have provided Declaration evidence explaining that the method of Michel et al. (or the goal of Michel et al.) does not remove other polyenes, etc., resulting in a composition or method of the current claims. It should be clear by a review of the record that Michel et al. fails to address amphotericin B compositions in terms of the removal of non-amphotericin B polyenes. Further, Michel et al.s' measurement of "residue on ignition" is not capable of distinguishing purity of the amphotericin. Applicants respectfully submit that the Examiner is simply focusing on the keyword "purity" without consideration of how Michels et al. are using the term. When reviewing the reference as a whole, as required, one of ordinary

skill in the art would reach a different view than the Examiner as to the conclusion of obviousness.

The second secondary reference, Tang, describes a method for using ion exchange chromatography to remove gram positive and gram negative bacteria from a methanolic suspension of antibiotics (including, amphotericin B) and bacteria. On the basis of Michel's terminology, the process of Tang is one of decontamination, not purification. As stated in the record, one of ordinary skill in the art would recognize that the method of Tang would not address separation of amphotericin B from other polyene antibiotics.

Thus, it is clear that the Examiner's overly general view that "...purification of amphotericin B was well known in the art..."does not work in the present case. One of ordinary skill in the art wound understand that so-called "purification methods" can not all be lumped into the same category and be expected to achieve the same results. Additionally, one of ordinary skill in the art would understand the present issue is not a "traditional" purification issue, where one would simply purify a product to expect better results. As emphasized in the record and at the interview, to date the source of the side effects of USP amphotericin B compositions was not known. It was the present inventors that discovered non-amphotericin B polyenes are a significant side effect source. In hindsight, one of ordinary skill in the art would view this case as being one of formulating a new amphotericin B product when compared to the USP products available – one that does not comprise as many harmful polyenes.[2]

[2] Applicants asked the Examiner to consider this point in the Response filed November 9, 2007. There, Applicants compared the present case to prior "purification" published decisions. See, for example, *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966). In the *Cofer* decision, claims to a free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of

The bottom line is that the prior art does not accomplish the present invention.

One of ordinary skill in the art would also understand the superior and unexpected results of the present invention. As shown in Declaration evidence (and journal article evidence) provided by Applicants, the compositions of the present invention, when compared to prior art preparations, demonstrated an ability to apply a 10-fold higher dose and obtain only about half the renal toxicity. Additionally, the Declaration shows that the mortality rate in infected mice treated with the claimed invention was about half the mortality rate of mice treated with commercial, USP preparations. Additionally, this trend occurs despite the 10-fold greater dose of the composition of the present invention.

In summary, Applicants respectfully submit that there should be no doubt that one of ordinary skill in the art would recognize the differences between the prior art and the present invention, recognize that the prior art failed to address the problem solved by the present invention, and recognize that the present invention provides superior and unexpected results when compared to the prior art.

There were three issues raised in the interview that can be clarified herein. First, the Examiner raised a question concerning the "starting point." That is, the Examiner had questions concerning USP formulations amphotericin B compositions that are presently used, and USP formulations. Secondly, the Examiner raised a question concerning the comparative testing

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record did not suggest the claimed compound in crystalline form or how to obtain such crystals. Applicants respectfully submit that the facts of the present case are comparable to those in *Cofer*. The prior art fails to disclose or suggest the claimed amphotericin B compositions, including compositions that are free from non-amphotericin B polyene compounds or endotoxin compounds.

presented in the record. Thirdly, the Examiner raised a question concerning the toxicity data discussed by Applicants.

(a) With respect to traditional amphotericin B formulations, Applicants have stated multiple times in the record that when compared to commercial, USP amphotericin B formulations, the compositions of the present invention exhibit superior and unexpected results, including many fewer devastating side effects.

Commercially available, USP amphotericin B formulations contains up to 25% impurities, including multiple polyene components. Unlike most drugs, which have impurity levels less than 1%, amphotericin B is not a single compound with very low impurity levels. See the Specification (including Examples 5 and 6, discussed below), and *J. Antiomicro Chemother* 2007 60(6): 1331-1340.

The National Formulary of the United States Pharmacopeia (the "USP") recognizes this. As per the USP, amphotericin B formulations can have a potency of not less than 750 micrograms in 1 mg of material, a purity of 75%. The USP monograph is attached (Attachment 1). Despite the fact that amphotericin B, USP may contain only 75% of the polyene compound known as amphotericin B, it is commonly referred to as, probably for simplicity's sake, "amphotericin B."

At points in the prosecution, even Applicants may have as well (including "parent" amphotericin B or "generic" amphotericin B). In fact, the formulations may be more accurately described as compositions that comprise an amphotericin B compound and other polyenes. In order to remedy any confusion, Applicants can clarify that the compositions of the present

invention are free from the described contaminants at the described levels.

The "parent" composition of the prior art is believed to be FUNGIZONE, supplied by E.R. Squibb & Sons, Inc. See Lopez-Burnstein at col. 1, lines 48-54 and Example 2. There is no indication it is a formulation that fails to comply with USP standards. See the official FDA information on FUNGIZONE (Amphotericin B For Injection, USP) available from drugs.com (Aattachment 2). Also, see the Physician's Desk Reference information on FUNGIZONE cream (Amphotericin B cream, USP) and FUNGIZONE intravenous (Amphotericin B for injection, USP) (Attachment 3).

Also see related USP formulations VHA, Pharma-Tek, Apotehcon, and Sigma discussed in the *J. Antiomicro Chemother* publication. Being USP formulations, they all comprise the harmful contaminants removed by the present invention.

The above "starting point" information should help the Examiner understand the deficiencies of the Office's position. Starting with a USP formulation, it should be clear that the asserted "purification" methods do not arrive at the present invention. Four-solvent methods, encapsulation methods, crystallization methods, ion-exchange chromatography, etc, all have missed the boat. For all its usefulness, USP amphotericin B formulations remain dangerous. As stated in the record, the prior art methods did not even know *what* caused the problems, much less how to address them.[3]

[3] Additionally, the present amendment should make it more clear to the Examiner that embodiments of the present invention are directed to an increased presence of the amphotericin B *compound*, distinguishable from the USP amphotericin B compositions with their higher content of impurities.

(b) With respect to comparative testing, the Examiner has implied (as did the outstanding Office Action) that the testing by Applicants "...fails to provide any actual experiments to support said statements [of superior and unexpected results]..." Applicants submit that this is not the case. As explained during the interview, the Examiner appears to be incorrectly viewing this case as a more simple, traditional "purification" case. Applicants have contended that the methods of the prior art, if employed, would not lead to the compositions of the present invention.

The first Kramer Declaration provides evidence that the purification process of the cited prior art would not or could not result in a product having the claimed purity levels. See paragraph 10 of the February 6, 2009, Kramer Declaration: "The method of Michel neither changed the composition nor the relative abundance of any of the individual components in the antibiotic (amphotericin B)." Paragraph 12: "From a review of this reference, one of ordinary skill in the art would understand that the disclosed ion exchange column process would not result in the features claims." Paragraph 14: "Thus, the method of Tang addressed a fundamentally different process than removal of polyenes and other soluble compounds that are present as impurities from amphotericin B..."

In summary, Applicants have shown that after the so-called purification processes of the secondary references, one would still have substantially the same content of amphotericin B *compound* as was present in the parent compound. Quite frankly, this complies with the Examiner's request and supplies the Examiner with the declaration evidence necessary to understand the deficiencies of the prior art. As stated in the Record, the Examiner has provided

no evidence to refute Applicants' position even though the method employed improperly shifts the burden of persuasion to the Applicants.

(c) The Examiner's question concerning the toxicity data discussed by Applicants throughout the Record (including in the Cleary Declaration), is believed to be resolved when it was discovered that the Examiner had not reviewed the *Journal of Antimicrobial Chemotherapy* publication that was discussed in, and attached to, the Cleary Declaration. The publication was discussed during the interview and a copy was left with the Examiner.

The Declaration evidence, when combined with data presented in the publication, showed that when compared to commercial, USP preparations, the present invention demonstrated an ability to apply a 10-fold higher dose and obtain only about half the renal toxicity. The Declaration further showed that the mortality rate in infected mice treated with the claimed invention was about half the mortality rate of mice treated with commercial, USP preparations. This rate occurred despite the 10-fold grater dose of the composition of the present invention. Not only does this result reinforce the long-felt need aspects of a safer treatment, but in addition shows the unexpected and superior results of the present invention.

The Examiner commented at the interview that the *Journal of Antimicrobial Chemotherapy* publication presented the data in a form approved by her to demonstrate the superior and unexpected results of the present invention. If this is not the case, the Examiner is invited to contact Applicants' representative immediately.

Secondary Considerations

In addition to the lack of a *prima facie* case of evidence, there is additional secondary evidence to be considered by the USPTO.

In the response filed February 12, 2009, detailed evidence was presented as secondary evidence, especially evaluating the long-felt need of the present invention. Secondary evidence must be evaluated by the USPTO when considering a case of obviousness. In the present case, it was not fully evaluated.

For the convenience of the Examiner, it is summarized herein.

It should be known by the Examiner that traditional amphotericin B induces serious adverse reactions. Yet, today (and for the past 40 years) amphotericin B remains the best or only alternative for critically ill patients.

Additionally, Applicants presented excerpts from Amphotericin labeling. These excerpts included warnings that although "Amphotericin B is frequently the only effective treatment available for potentially life-threatening fungal disease. In each case, the use of amphotericin B and "its possible life-saving benefit must be balanced against its untoward and dangerous side effects." See the February 12, 2009 Response at page 17-18. Also, the label warned that amphotericin B "...should be reserved for treatment of patients with progressive, potentially life-threatening fungal infections due to susceptible organisms..."Id.

Additionally, there is another long-felt need addressed by the present invention. The cost to the patient of amphotericin B is extremely expensive. See paragraph 11 of Dr. Cleary's Declaration of November 28, 2008:

The cost of AmB-induced events was $29,823 per case. The use of lipid-based formulations of AmB, secondary to their lower risk for nephrotoxicity, is replacing conventional AmB therapy for treatment of systemic fungal infection except in many HIV-infected and pediatric patients. Yet, the cost of comparable therapy is considerably greater for the lipid formulation; daily cost for AmB averages $25, whereas that for lipid-formulated AmB ranges between $450 and $1850. Assuming a 14-day course of therapy, a patient will pay an average of $7000 more for a lipid-based, albeit safer, AmB product. Thus, the present invention can provide a significant improvement over what is currently available. Given the superior and unexpected improvements of the present invention over previous attempts to make AmB treatment safer, the present invention can potentially increase the number of treatment candidates, and allow for increased dosages with reduced side effects.

In response to the secondary evidence, the outstanding Office Action summarily states that "Applicant also contends that traditional amphotericin B induces serious adverse reactions. This argument has not been found persuasive since no comparison of amphotericin B purified by the references' methods and the claimed amphotericin has been presented." See the Office Action at pages 4-5.

This position is flawed for at least two reasons. First, the Office Action has failed to set forth a valid reason for doubting the evidence presented by Applicants as to the adverse reactions of amphotericin B.[4] Additionally, the Office Action failed to identify one reason why the "references' method" - encapsulation method of the Lopez-Berestein primary reference (filed in

[4] If the position of the Examiner is that Applicants have not been persuasive as to their contention that "traditional amphotericin B induces serious adverse reactions..." this position flies in the face of mountains of evidence, including amphotericin B formulation labeling itself. Perhaps clarification of this statement is in order since without supporting evidence (the Office Action presents none), this position would be simply incredible.

1984), the crystallization method of the Michel et al. secondary reference (filed in 1987), or the ion exchange method of the second secondary reference (filed in 1980) would lead one of ordinary skill in the art to doubt the dire warnings and dangers concerning modern-day amphotericin B treatment.

If anything, one of ordinary skill in the art would have the opposite view of the Office Action – that there have been the many prior attempts to formulate a safer amphotericin B product and that the techniques discussed in the prior art represent the failure of others to formulate a safer amphotericin product.

Summary

As a final points, the current claims should clarify that it it's the amphotericin B *compound* is present in the required amounts, as opposed to a "parent" or "generic" USP formulation, which includes additional non-amphotericin B polyene contaminants.

Additionally, as indicated above, claims 19-21 are free from any rejection. These claims should have been indicated as being allowed.

Finally, there are many aspects of Applicants previous responses that have not been addressed in subsequent Office Actions. The following is an non-exhaustive list:

- An argument in the previous response is that 95% and 96%, for example, are encompassed by, and supported by "greater than about 90%..." As indicated above, this was not addressed in the outstanding Office Action.
- There was no indication in the Office Action as to why the principles of In re

Wertheim would not indicate the claimed ranges comply with the written description requirement.

- With respect to the written description requirement in general, Applicants have repeatedly requested a specific, objective, reason that is supported by evidence as to why the claims fail to comply. To date, no reasons have been provided.
- The Supreme Court (Graham v. John Deere) and USPTO policy mandate that secondary considerations be considered. In this case, they were not addressed.
- Twice in the prosecution, Applicants have argued that the Cofer decision presented facts similar to those presented here (see footnote 2, above). To date, a contrary argument has not been presented.
- With respect to the more recent Aventis decision, Applicants explained how the present case is similar to circumstances where the Federal Circuit mentioned patentability may be found, such as where "it may not be known that a purified compound is present in or an active ingredient in a mixture..." See the Amendment filed November 9, 2007. Arguments as to why the Federal Circuit's reasoning wound not lean toward patentability of the present case are lacking.

Applicants respectfully submit that the record would be clearer, and prosecution more compact, if the above are clearly and objectively addressed by the Office.

Supervisory Patent Examiner Review Requested

As an Application having received its fifth office action, Applicant respectfully requests that the present Application be "carefully studied by the supervisory patent examiner" pursuant to

M.P.E.P. § 707.02. The statement in § 707.02 that "...supervisory patent examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them." is particularly relevant in the present application.

The time and cooperation of Supervisory Patent Examiner are greatly appreciated.

In view of the above, Applicant's respectfully submit that the rejections should be withdrawn and the present application allowed to issue.

Petition for Extension of Time

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants hereby petition for a three-month extension of time for filing a response to the outstanding Office Action. Payment for the extension of time fee is being submitted with the electronic filing of this response.

The Office is authorized to charge any deficiency or credit any overpayment associated with the filing of this application to Deposit Account 50-2752.

Finally, please contact the undersigned if there are any questions regarding this Amendment or the application in general.

Respectfully submitted,

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